DOCKET NO.: ALLE0027-100 (17641) **PATENT**

Amendment to the Specification

(I) On page 35 of the specification, under the word "Abstract", please delete the current paragraph, and insert the following paragraph:

The present invention provides methods for improving blood supply through a grafted blood vessel. In some embodiments, the methods comprise the step of locally administering a botulinum toxin to the grafted blood vessel, thereby improving blood supply through the grafted blood vessel.

(II) Please replace the paragraph on page 3, starting with line 8, with the following replacement paragraph to identify the generic terminology after the trademark BOTOX®:

Botulinum toxin type A is the most lethal natural biological agent known to man. About 50 picograms of a commercially available botulinum toxin type A (purified neurotoxin complex)[1] is a LD50 in mice (i.e. 1 unit). One unit of BOTOX® (a botulinum toxin type A purified neurotoxin complex, which is also referred to as a botulinum toxin type A complex) contains about 50 picograms (about 56 attomoles) of botulinum toxin type A complex. Interestingly, on a molar basis, botulinum toxin type A is about 1.8 billion times more lethal than diphtheria, about 600 million times more lethal than sodium cyanide, about 30 million times more lethal than cobra toxin and about 12 million times more lethal than cholera. Singh, *Critical Aspects of Bacterial Protein Toxins*, pages 63-84 (chapter 4) of Natural Toxins II, edited by B.R. Singh et al., Plenum Press, New York (1976) (where the stated LD50 of botulinum toxin type A of 0.3 ng equals 1 U is corrected for the fact that about 0.05 ng of BOTOX® (a botulinum toxin type A complex) equals 1 unit). One unit (U) of botulinum toxin is defined as the LD50 upon intraperitoneal injection into female Swiss Webster mice weighing 18 to 20 grams each.

(III) Please replace the footnote paragraph on page 3 with the following footnote paragraph to identify the generic terminology after the trademark BOTOX®:

[1]Available from Allergan, Inc., of Irvine, California under the tradename BOTOX® (a botulinum toxin type A complex) in 100 unit vials)

(IV) Please replace the paragraphs starting on page 10, beginning with line 17, through page 13, ending with line 5, with the following paragraphs to identify the generic terminology after the trademark BOTOX®:

A commercially available botulinum toxin containing pharmaceutical composition is sold under the trademark BOTOX® (available from Allergan, Inc., of Irvine, California). BOTOX® (a botulinum toxin type A complex) consists of a purified botulinum toxin type A complex, albumin and sodium chloride packaged in sterile, vacuum-dried form. The botulinum toxin type A is made from a culture of the Hall strain of Clostridium botulinum grown in a medium containing N-Z amine and yeast extract. The botulinum toxin type A complex is purified from the culture solution by a series of acid precipitations to a crystalline complex consisting of the active high molecular weight toxin protein and an associated hemagglutinin protein. The crystalline complex is re-dissolved in a solution containing saline and albumin and sterile filtered (0.2 microns) prior to vacuum-drying. The vacuum-dried product is stored in a freezer at or below -5°C. BOTOX® (a botulinum toxin type A complex) can be reconstituted with sterile, non-preserved saline prior to intramuscular injection. Each vial of BOTOX® (a botulinum toxin type A complex) contains about 100 units (U) of Clostridium botulinum toxin type A purified neurotoxin complex, 0.5 milligrams of human serum albumin and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

To reconstitute vacuum-dried BOTOX® (a botulinum toxin type A complex), sterile normal saline without a preservative; (0.9% Sodium Chloride Injection) is used by drawing up the proper amount of diluent in the appropriate size syringe. Since BOTOX® (a botulinum toxin type A complex) may be dispersed or denatured by bubbling or similar violent agitation, the diluent is gently injected into the vial. For sterility reasons BOTOX® (a botulinum toxin type A complex) is preferably administered within four hours after the vial is removed from the freezer and reconstituted. During these four

hours, reconstituted BOTOX® (a botulinum toxin type A complex) can be stored in a refrigerator at about 2° C. to about 8°C. Reconstituted, refrigerated BOTOX® (a botulinum toxin type A complex) has been reported to retain its potency for at least about two weeks. *Neurology*, 48:249-53:1997.

It has been reported that botulinum toxin type A has been used in clinical settings as follows:

(1) about 75-125 units of BOTOX® (a botulinum toxin type A complex) per intramuscular injection (multiple muscles) to treat cervical dystonia;

(2) 5-10 units of BOTOX® (a botulinum toxin type A complex) per intramuscular injection to treat glabellar lines (brow furrows) (5 units injected intramuscularly into the procerus muscle and 10 units injected intramuscularly into each corrugator supercilii muscle);

(3) about 30-80 units of BOTOX® (a botulinum toxin type A complex) to treat constipation by intrasphincter injection of the puborectalis muscle;

(4) about 1-5 units per muscle of intramuscularly injected BOTOX® (a botulinum toxin type A complex) to treat blepharospasm by injecting the lateral pre-tarsal orbicularis oculi muscle of the upper lid and the lateral pre-tarsal orbicularis oculi of the lower lid.

(5) to treat strabismus, extraocular muscles have been injected intramuscularly with between about 1-5 units of BOTOX® (a botulinum toxin type A complex), the amount injected varying based upon both the size of the muscle to be injected and the extent of muscle paralysis desired (i.e. amount of diopter correction desired).

(6) to treat upper limb spasticity following stroke by intramuscular injections of BOTOX® (a botulinum toxin type A complex) into five different upper limb flexor muscles, as follows:

(a) flexor digitorum profundus: 7.5 U to 30 U

(b) flexor digitorum sublimus: 7.5 U to 30 U

(c) flexor carpi ulnaris: 10 U to 40 U

(d) flexor carpi radialis: 15 U to 60 U

(e) biceps brachii: 50 U to 200 U. Each of the five indicated muscles has been injected at the same treatment session, so that the patient receives from 90 U to 360 U of upper limb flexor muscle BOTOX® (a botulinum toxin type A complex) by intramuscular injection at each treatment session.

(7) to treat migraine, pericranial injected (injected symmetrically into glabellar, frontalis and temporalis muscles) injection of 25 U of BOTOX® (a botulinum toxin type A complex) has showed significant benefit as a prophylactic treatment of migraine compared to vehicle as measured by decreased measures of migraine frequency, maximal severity, associated vomiting and acute medication use over the three month period following the 25 U injection.

It is known that botulinum toxin type A can have an efficacy for up to 12 months (*European J. Neurology* 6 (Supp 4): S111-S1150:1999), and in some circumstances for as long as 27 months, when used to treat glands, such as in the treatment of hyperhydrosis. See e.g. Bushara K., *Botulinum toxin and rhinorrhea,* Otolaryngol Head Neck Surg 1996;114(3):507, and *The Laryngoscope* 109:1344-1346:1999. However, the usual duration of an intramuscular injection of BOTOX® ~~Botox®~~ (a botulinum toxin type A complex) is typically about 3 to 4 months.

The success of botulinum toxin type A to treat a variety of clinical conditions has led to interest in other botulinum toxin serotypes. Two commercially available botulinum type A preparations for use in humans are BOTOX® (a botulinum toxin type A complex) available from Allergan, Inc., of Irvine, California, and ~~Dysport®~~ DYSPORT® (a botulinum toxin type A complex) available from Beaufour Ipsen, Porton Down, England. A Botulinum toxin type B preparation (MYOBLOC®) ~~(MyoBloc®)~~ is available from Elan Pharmaceuticals of San Francisco, California.

(V) Please replace the paragraphs starting on page 23, line 1, through page 24, line 4, with the following paragraphs to identify the generic terminology after the trademark BOTOX®, DYSPORT®, and MYOBLOC®:

The amount of a botulinum toxin administered according to a method within the scope of the disclosed invention can vary according to the particular characteristics of the vascular disorder being treated, including its severity and other various patient variables including size, weight, age, and responsiveness to therapy. To guide the practitioner, typically, no less than about 1 unit and no more than about 50 units of a botulinum toxin type A (such as BOTOX®, a botulinum toxin type A complex) is administered per injection site (i.e. to each vascular disorder location injected), per patient treatment session. For a botulinum toxin type A such as DYSPORT® (a botulinum toxin type A complex), no less than about 2 units and no more about 200 units of the botulinum toxin type A are administered per administration or injection site, per patent treatment session. For a botulinum toxin type B such as MYOBLOC® (a botulinum toxin type B preparation), no less than about 40 units and no more than about 2500 units of the botulinum toxin type B are administered per administer or injection site, per patient treatment session. Less than about 1, 2 or 40 units (of BOTOX® (a botulinum toxin type A complex), DYSPORT® (a botulinum toxin type A complex) and MYOBLOC® (a botulinum toxin type B preparation) respectively) can fail to achieve a desired therapeutic effect, while more than about 50, 200 or 2500 units (of BOTOX® (a botulinum toxin type A complex), DYSPORT® (a botulinum toxin type A complex) and MYOBLOC® (a botulinum toxin type B preparation) respectively) can result in clinically observable and undesired muscle hypotonicity, weakness and/or paralysis.

More preferably: for BOTOX® (a botulinum toxin type A complex) no less than about 2 units and no more about 20 units of a botulinum toxin type A; for DYSPORT® (a botulinum toxin type A complex) no less than about 4 units and no more than about 100 units, and; for MYOBLOC® (a botulinum toxin type B preparation), no less than about 80 units and no more than about 1000 units are, respectively, administered per injection site, per patient treatment session.

Most preferably: for BOTOX® (a botulinum toxin type A complex) no less than about 5 units and no more about 15 units of a botulinum toxin type A; for DYSPORT® (a botulinum toxin type A complex) no less than about 20 units and no more than about

75 units, and; for MYOBLOC® (a botulinum toxin type B preparation), no less than about 200 units and no more than about 750 units are, respectively, administered per injection site, per patient treatment session. It is important to note that there can be multiple injection sites (i.e. a pattern of injections) for each patient treatment session.

(VI) Please replace the paragraph of Example 1 on page 28, with the following paragraph:

A patient ~~can receive~~ receives a kidney transplant. Prior to or concurrently with the kidney transplant, 1 to 50 unit of a botulinum toxin type A is ~~can be~~ injected into the wall of the renal artery in proximity to the transplanted kidney in order to prevent the constriction of the renal artery after the transplant. The patient ~~can~~ thereby exhibits ~~exhibit~~ normal blood flow through the renal artery after the transplant.

(VII) Please replace the paragraph of Example 2 on page 28, with the following paragraph:

A female patient age 26 presents ~~present~~ with a diagnosis of Raynaud's syndrome. The skin of her fingers and toes exhibits a patchy red color. A total of 100 units of a botulinum toxin is injected subdermally (5 units into each of her 20 digits) into each finger and toe. Within two week her symptoms regresses ~~have regressed~~, her skin returns to a normal hue and she remains symptom free for 3 to 4 months.

(VIII) Please replace the paragraph of Example 3 on page 29, with the following paragraph:

A male patient age 55 experiences ~~experienced~~ sudden headache after subarachnoidal bleeding from a ruptured aneurysm of the left middle cerebral artery. Because of a symptomatic hydrocephalus, a ventricle drainage via catheter can be performed. Three days after the bleeding he develops ~~can develop~~ a mild hemiparesis and transcranial Doppler sonography identifies ~~identified~~ vasospasms of both middle and anterior cerebral arteries. Intrathecal administration of botulinum toxin type B via the ventricle catheter leads ~~can led~~ to a marked reduction of vasospasms within 48 hours as

the ~~documented by~~ Doppler sonography shows. MRI does ~~can~~ not show any ischemic lesion of the brain. He ~~can~~ completely recovers ~~recover~~ without any neurological deficits.

(IX) Please replace the first paragraph of Example 4 on page 29, with the following paragraph:

A patient 67 undergoes preparation ~~is prepared~~ for a coronary artery bypass graft (CABG). The patient develops ~~has developed~~ atherosclerosis in his coronary arteries, the flow of blood through these vessels is blocked, and the blood supply to heart muscle is jeopardized. Prognosis is a heart attack or sudden death. The CABG operation is designed to re-route the blood around these blockages to prevent a heart attack or sudden death. Conventionally, with this patient an artery from behind the breast bone, and veins from the legs is used to bypass the blood around the coronary artery blockages.